Open questions

Great organizing principles
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In this column, Lewis Wolpert raised the question of whether there remain any new principles to be discovered in biology [1]. He invented the good fairy godmother of science (GOOFGOOS), to whom we may pose one or two of our most pressing questions of general principle. Horace Barlow raised the further question of whether biology will ultimately be found reducible to a few universal principles, like the great conservation laws of physics, or whether instead biology will have a multiplicity of principles like the trees in a forest [2].

I have been asked to reflect on these questions from the perspective of structural biology. I believe many, perhaps most, of the interesting principles remain to be discovered, but I don't think there will be either a few or a multiplicity. I believe there will be a hierarchical network of principles at all levels of biology — more like a multidimensional pyramid — just as there are in chemistry and physics. For example, the Second Law of Thermodynamics must be near the top of such a pyramid, the hydrophobic effect further down, and lower and to the side is how proteins fold.

In addition to this question of the organization of principles is that of the 'principles of organization'. Although Wolpert says my question should be answerable in less than 30 words, I would like the GOOFGOOS to provide me with a textbook on Great Organizing Principles in Biology. Like a good physical chemistry text, I want it full of examples, illustrations and worked problems. It will tell us how to design new forms of complex organization, say new life forms, using a range of different building blocks, say polymeric backbones that are not based on peptide or nucleotide units.

Chapter 1 will describe intermolecular interactions in solution, accurately rather than in terms of the approximate models currently available. Chapter 2 will describe folding codes for designing polymers that will fold in protein-like ways, recipes for choosing informational polymers like DNA and RNA, and tips on how to get tertiary interactions where you want them. Chapter 3 will show how to predict biomolecular binding, induced fit and other conformational changes. Chapter 4 will show how to design biomolecular interfaces and processes of regulation and allostery. Chapter 5 will describe the principles of self-assembly of these single-molecule components into complexes and ultimately into organelles; and chapter 6 how to make cells as networks of interacting biomolecules. Chapter 7 will describe principles of organization of cells into organs, and chapter 8 the dynamics of it all — molecular evolution, cellular development — based on principle, not speculation. My hope is that engineers will use this book to design very smart new materials.

Without the GOOFGOOS, I doubt this text will be available soon, as self-organization is poorly understood. We have some understanding of how simple colloids and polymers organize into planes, spheres, and crystals, but biological organization is hugely different. It involves objects that talk, think, create, evolve, and do science. How does a solution of nucleotides, amino acids, sugars and water reach such extraordinary heights of organization? How does purposeful, reproductive, adaptive, goal-oriented behavior emerge from interacting molecules?

Though we're nowhere near answering these questions, at least two of the 'great organizing principles' at the top of the pyramid are already fairly evident, and have a universality that transcends physics, chemistry and biology [3]. The Second Law of Thermodynamics states that systems tend to optimize cost functions (energy), balanced against a tendency toward disorder. This, with Darwin's principle that the fittest components can best survive evolutionary processes, underpins some simple observations of self-organization. For instance, Eigen and Schuster modelled chemical hypercycles [4], where molecules that catalyze their own creation can cooperate or compete with other molecules for resources. At the next level up, specialized cell types recruit others, assemble into cooperative hierarchies, and form divisions of labor that compete with other such systems.

This is a start, but we need the GOOFGOOS's book to provide us with middle-level principles that connect the grand principles to daily observations in molecular biology. For example, how does the simplest goal-seeking behavior, the minimization of a free energy, lead to increasingly complex goal-seeking behaviors? How do complexes of molecules or cells organize so as to optimize their division of labor? What is a better property than entropy to measure how biological organization develops?

I am hoping the GOOFGOOS will provide quantitative models, maybe sets of differential equations, or artificial life simulations, into which I can put the boundary conditions of interest to me, insert my favorite component molecules, integrate from time zero to a billion years, and compute all kinds of properties about the molecular associations and the community of cells that emerge — their sizes, diets, conflicts, agonies and defeats. I hope to eavesdrop as they pose their own questions to the GOOFGOOS.

References
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